

Age-Related Macular Degeneration

Pathogenesis • Morphology • Clinicopathologic Correlation

Dry (atrophic) and wet (neovascular) phenotypes

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Identify the macular support unit that maintains photoreceptor function.
- Distinguish dry AMD from wet AMD by vascular morphology.
- Explain complement-associated geographic atrophy and neovascular injury.
- Relate morphologic lesions to symptoms, imaging, and treatment targets.

Concept → lesion

A tissue-level mechanism explains both morphology and visual dysfunction.

Why macular damage matters

- The macula supports high-resolution, straight-ahead vision.
- Loss of macular function particularly compromises central visual tasks.
- Damage may involve neural retina, RPE, or its vascular support.
- AMD is a major cause of central visual impairment in later life.

Central vision

A small retinal region carries a disproportionate functional burden.

The macula in retinal organization

Neurosensory retina

Photoreceptors translate light into neural signals for vision.

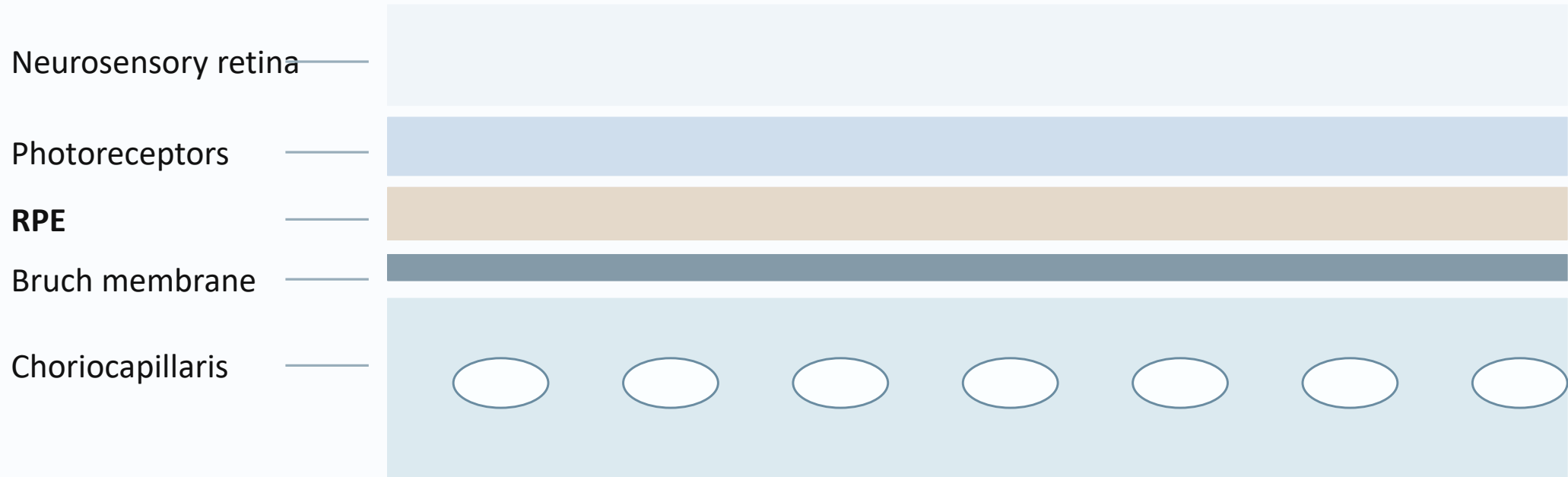
Macula

Central retinal region critical for detailed straight-ahead sight.

Choroid

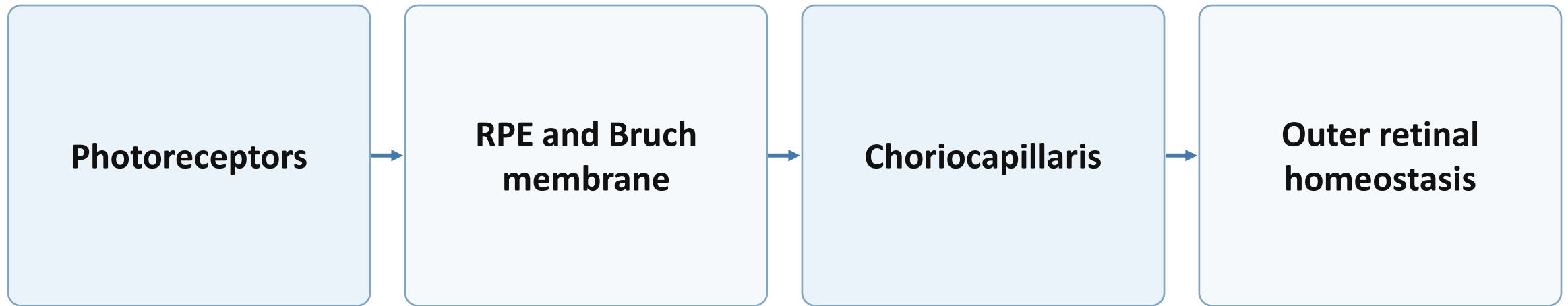
Outer-retinal vascular support supplied through the choriocapillaris.

RPE–Bruch membrane–choriocapillaris unit



Schematic — not a tissue section or OCT image

Photoreceptors depend on underlying support



Disruption of one component can compromise the cells above it.

Why the RPE cannot be considered in isolation

- The RPE lies directly beneath photoreceptor outer segments.
- Its basement membrane contributes to Bruch membrane.
- The RPE is coupled anatomically and functionally to the choriocapillaris.
- Loss of any linked component threatens overlying photoreceptors.

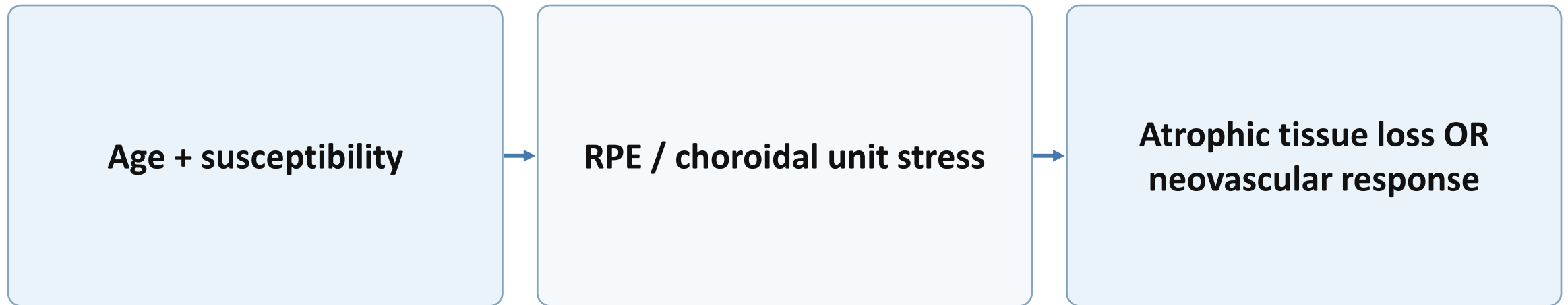
Functional unit

Neural, epithelial,
extracellular and vascular
compartments act together.

Two forms of AMD have different vascular behavior

Feature	Dry (atrophic)	Wet (neovascular)
Neoangiogenesis	Absent	Present
Core lesion	Drusen / geographic atrophy	Choroidal neovascular membrane
Dominant injury	Tissue loss	Leakage, bleeding, scarring
Visual consequence	Atrophy-associated dysfunction	Exudative or hemorrhagic dysfunction

Atrophy and neovascularization are distinct routes



One phenotype is not an obligatory antecedent of the other.

Dry and wet AMD may coexist

- A patient may exhibit atrophic and neovascular features.
- The dry phenotype is not a necessary precursor to wet AMD.
- The two forms have distinct pathobiologic event sequences.
- Classifying the current lesion requires attention to neovascularization.

No fixed sequence

Coexistence does not imply a single obligatory linear progression.

Advancing age is a major determinant

- AMD risk increases with advancing age.
- The disease burden rises as populations live longer.
- The source describes AMD among older adults as an important health problem.
- Age acts alongside inherited susceptibility and environmental exposure.

Age

Age changes the context in which other risk mechanisms operate.

Genetic predisposition contributes to AMD

- Susceptibility is associated with polymorphisms in complement regulatory genes.
- CFH and CFI are emphasized.
- An associated variant changes risk; It does not establish a monogenic diagnosis.
- Molecular predisposition interacts with aging and environmental factors.

Risk variants

The textbook frames AMD as a complex, multifactorial condition.

Smoking adds an environmental risk

- Cigarette smoking is identified as a potential AMD risk factor.
- The association is especially relevant in genetically predisposed individuals.
- Environmental exposures should be considered alongside inherited risk.
- Smoking is a modifiable factor for risk counseling.

Modifiable exposure

A gene–environment perspective better fits AMD than genetic determinism.

Oxidative stress participates in the disease model

Aging

Long-term biologic stresses accumulate with age.

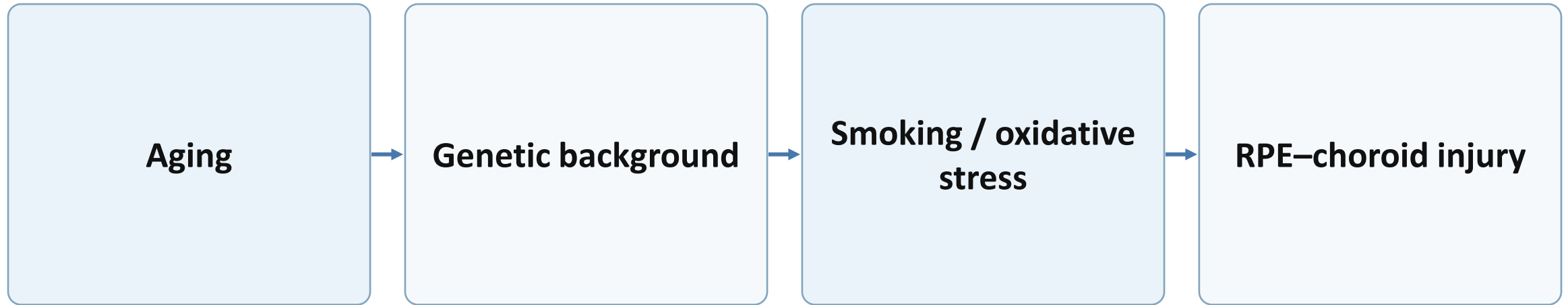
Oxidative stress

Named among the pathogenic risk factors in the Robbins schematic.

Complement activation

Links local inflammatory injury to the atrophic phenotype.

Multiple risk pathways converge on one tissue unit



This is a conceptual risk integration, not a quantitative causal model.

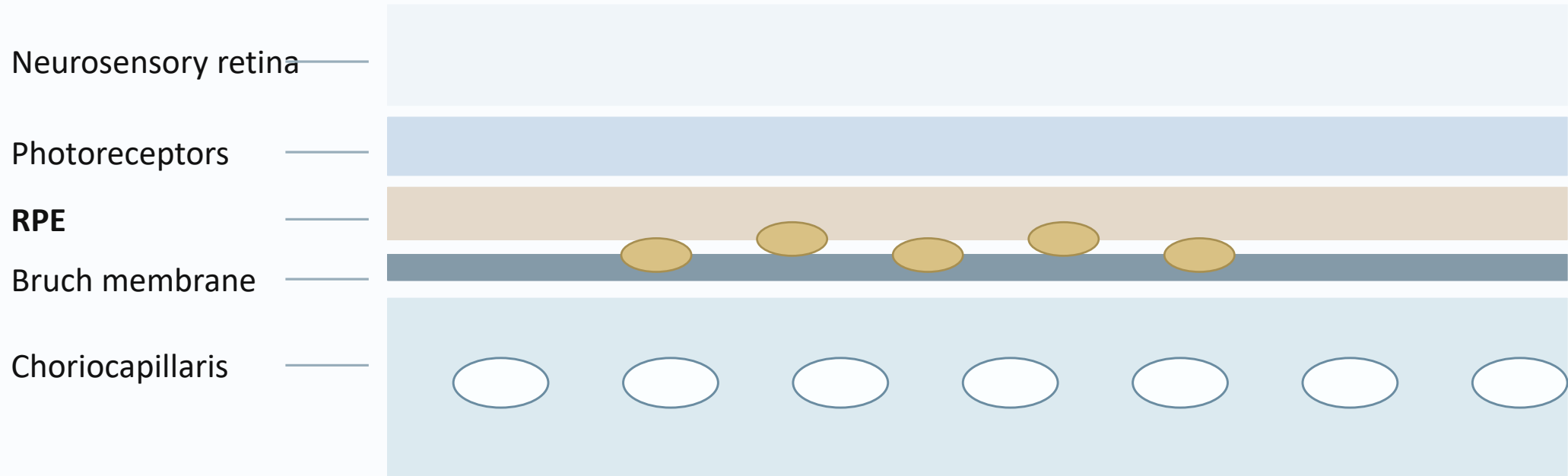
Drusen are deposits associated with dry AMD

- Diffuse or discrete deposits in Bruch membrane.
- These deposits are termed drusen.
- Drusen reflect extracellular material accumulation at the RPE–Bruch interface.
- They are a morphologic feature of the atrophic phenotype.

Drusen

Localization within the supporting membrane is the key histologic fact.

Drusen at the RPE–Bruch interface



Schematic — not a tissue section or OCT image

How to recognize the pathologic significance of drusen

Site

Drusen are deposits associated with Bruch membrane.

Morphology

Deposits can be diffuse or discrete rather than uniformly distributed.

Interpretation

A druse is a lesion of support tissue, not new blood-vessel growth.

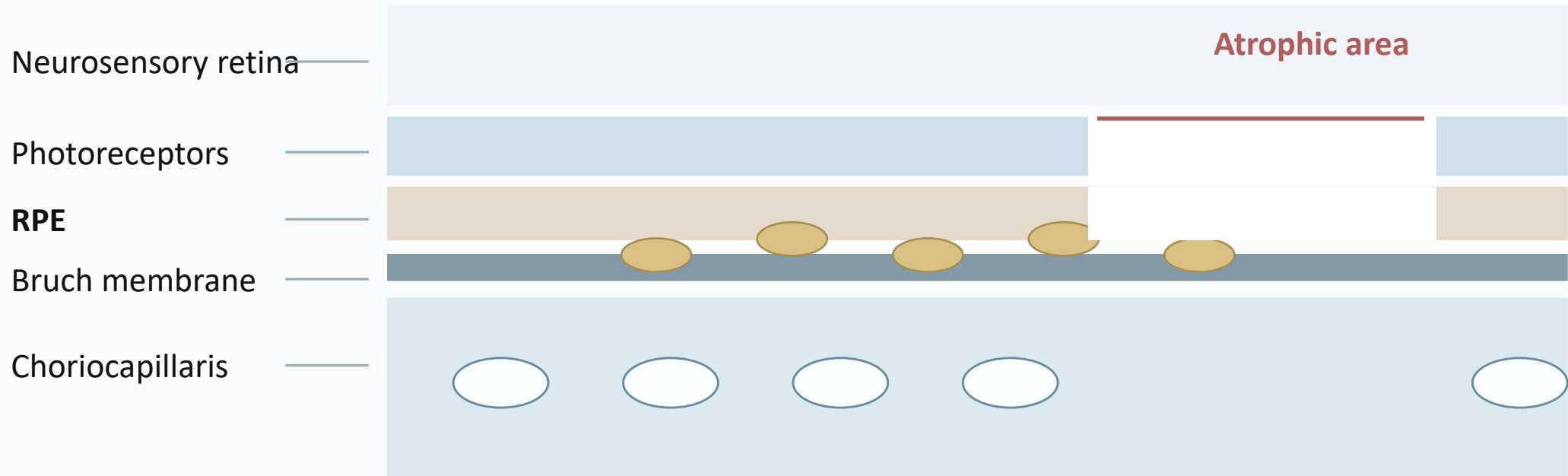
The dry phenotype includes tissue atrophy

- Dry AMD is defined in the source by drusen and geographic atrophy of the RPE.
- The atrophic lesion affects more than pigment epithelium alone.
- Photoreceptors and underlying choriocapillaris may also be lost.
- The spatial distribution of atrophy governs its visual impact.

Geographic atrophy

Atrophy represents loss of components of the outer-retinal unit.

Geographic atrophy: A focal tissue-loss lesion



Schematic — not a tissue section or OCT image

Three tissue losses explain geographic atrophy

RPE

Atrophy removes support immediately beneath photoreceptors.

Photoreceptors

Loss of light-sensitive cells directly compromises function.

Choriocapillaris

Loss of local vascular support accompanies advanced atrophy.

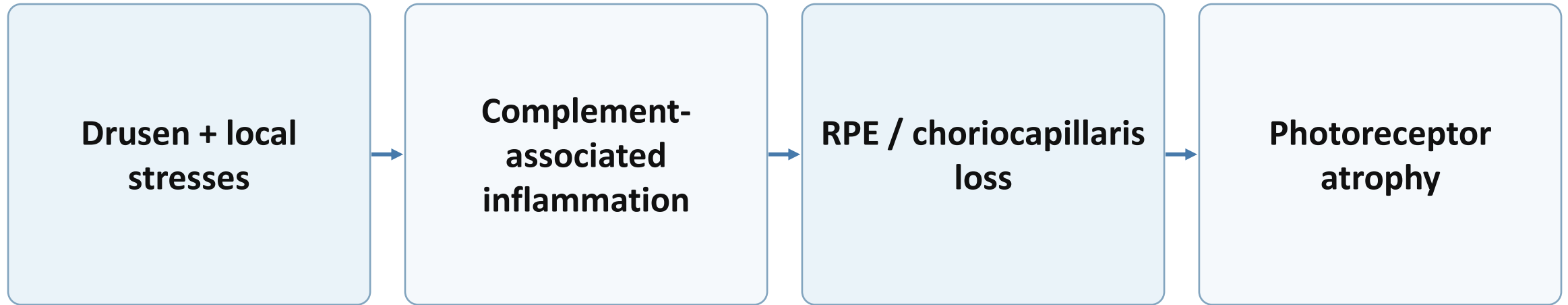
The macular location determines visual severity

- Photoreceptor loss contributes directly to impaired central vision.
- RPE depletion compromises the outer retinal support system.
- Choriocapillaris atrophy adds loss of vascular support.
- Vision loss can be severe when critical macular structures are involved.

Lesion → deficit

The location and extent of outer-retinal injury matter clinically.

Dry AMD: A pathway to geographic atrophy



Conceptual pathway; The full mechanism remains incompletely resolved.

Complement is central to the atrophic phenotype

- Geographic atrophy with chronic complement activation.
- Excess complement activity is linked to injury within the macular unit.
- CFH and CFI represent regulatory components in this system.
- The exact downstream mechanism of photoreceptor injury is not fully known.

Chronic activation

Complement dysregulation is a mechanistic association, not a complete account.

Complement regulation balances tissue defense

Activation

Complement can amplify immune responses.

Regulation

Regulatory factors limit inappropriate amplification.

Dysregulation

Reduced restraint may contribute to tissue-damaging inflammation.

CFH is a regulator associated with AMD risk

- CFH encodes complement factor H.
- Variants affecting this regulatory system are associated with AMD risk.
- The mechanistic framework is excessive complement activity.
- Association does not specify which patient will progress to atrophy.

CFH

Complement regulation is a susceptibility pathway, not a stand-alone diagnostic test.

CFI belongs to the same susceptibility network

- CFI encodes complement factor I.
- CFI among AMD-associated complement regulatory genes.
- Its relevance reinforces a pathway-level disease model.
- Inherited risk factors operate alongside non-genetic exposures.

CFI

Several risk loci can implicate the same biologic pathway.

Complement polymorphisms do not equal causation

- A genetic association identifies increased disease susceptibility.
- The polymorphism alone is not proof that AMD is present.
- Pathologic diagnosis relies on ocular phenotype rather than genotype alone.
- The precise injury pathway downstream of complement remains uncertain.

Risk ≠ diagnosis

Avoid a deterministic interpretation of susceptibility variants.

An important mechanistic uncertainty remains

Established

Complement-related gene associations and inflammation accompany AMD.

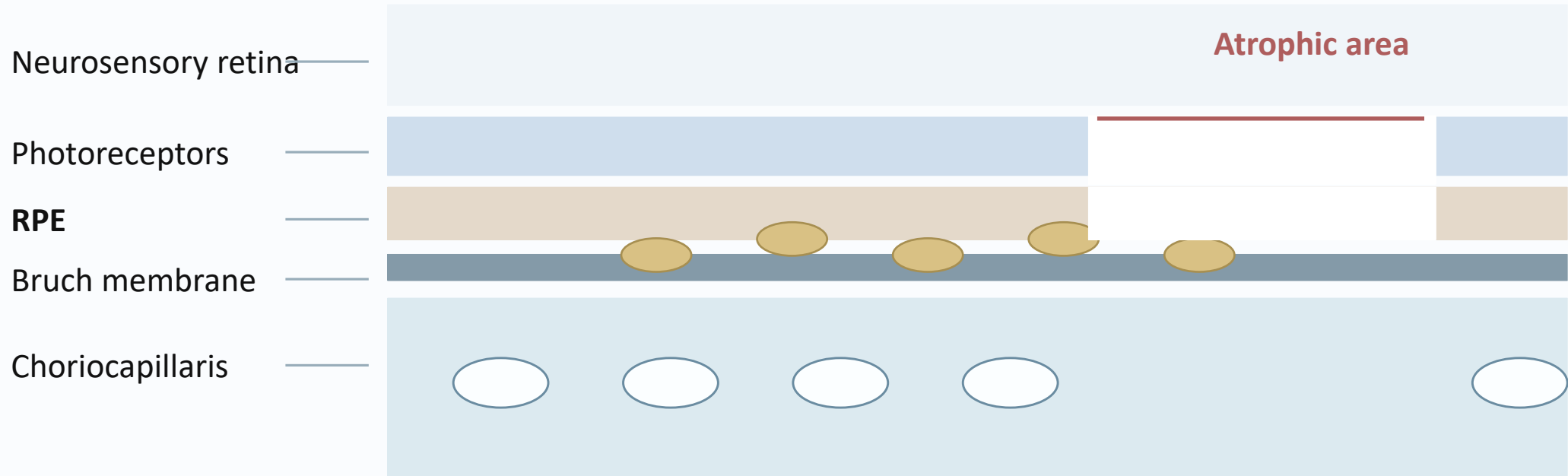
Probable model

Excess complement activity contributes to retinal-unit injury.

Unresolved

How this activity directly injures photoreceptors is not fully elucidated.

Dry AMD: Integrated anatomic mechanism



Schematic — not a tissue section or OCT image

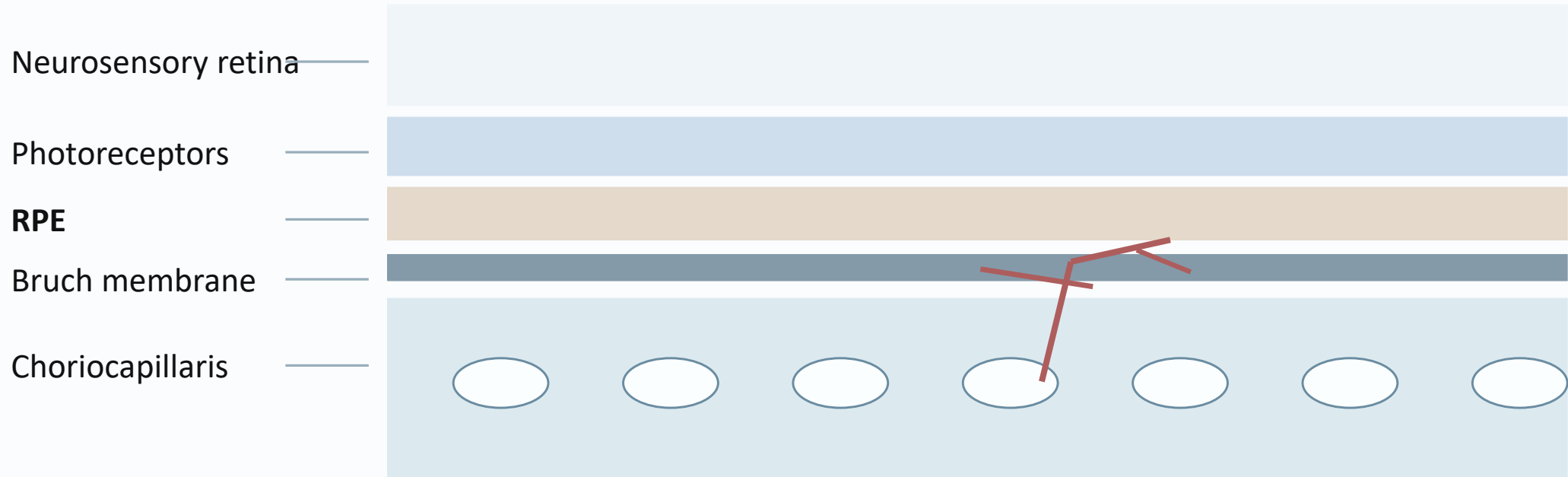
Wet AMD is defined by neovascularization

- Neovascular AMD is also termed exudative or wet AMD.
- Its key lesion is a choroidal neovascular membrane.
- Neovessels are presumed to arise from the choriocapillaris.
- Abnormal vessel permeability and bleeding drive additional damage.

Defining lesion

Neovascularization separates wet AMD from the atrophic phenotype.

Choroidal vessels breach Bruch membrane



Schematic — not a tissue section or OCT image

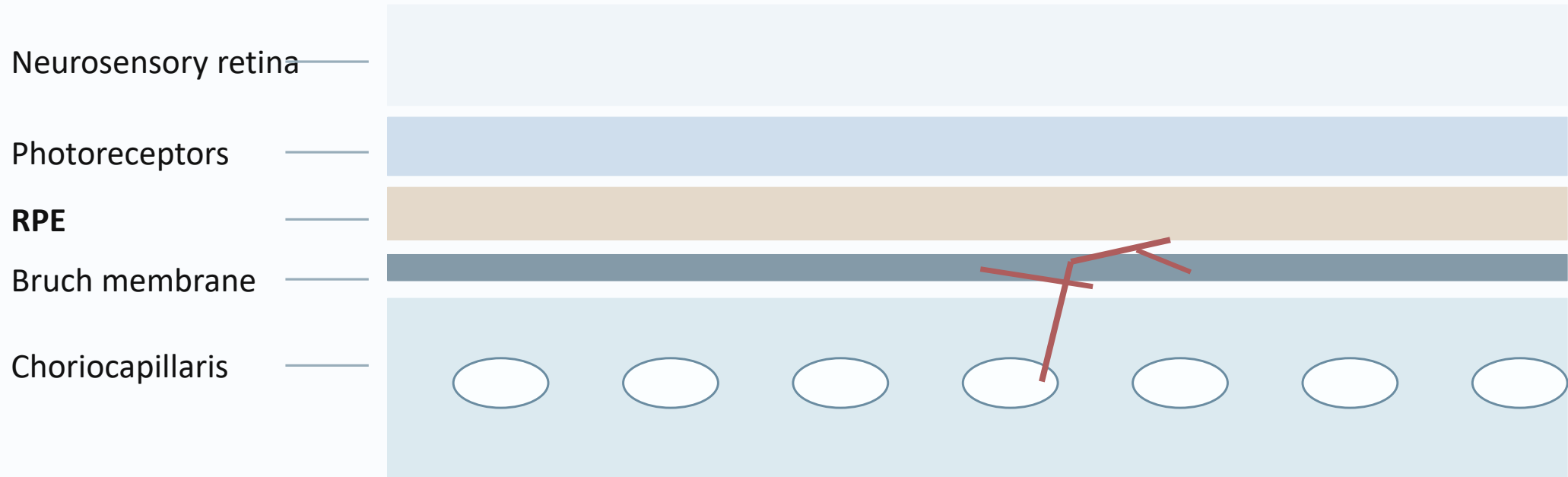
The choriocapillaris is the proposed vessel source

- The normal choriocapillaris lies beneath Bruch membrane.
- Neovascular vessels are thought to originate within this vascular layer.
- They cross Bruch membrane into a normally avascular compartment.
- The membrane initially may lie beneath the RPE.

Direction matters

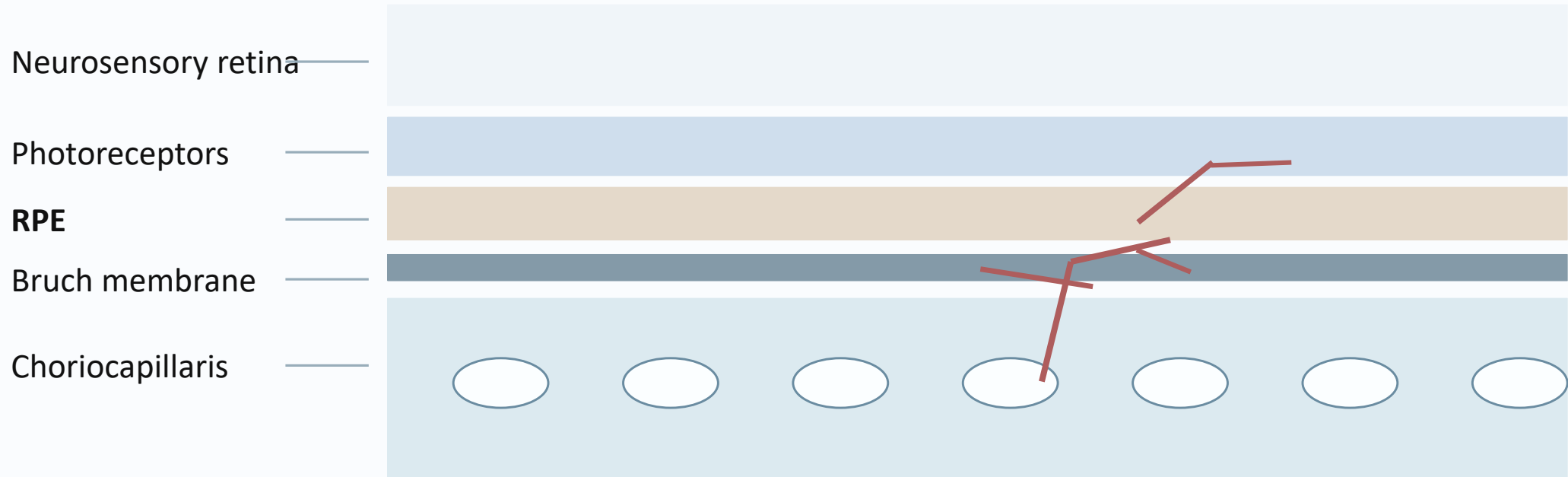
Choroid → Bruch membrane
→ sub-RPE space.

Sub-RPE neovascular membrane is an early location



Schematic — not a tissue section or OCT image

Neovessels may extend beneath the retina



Schematic — not a tissue section or OCT image

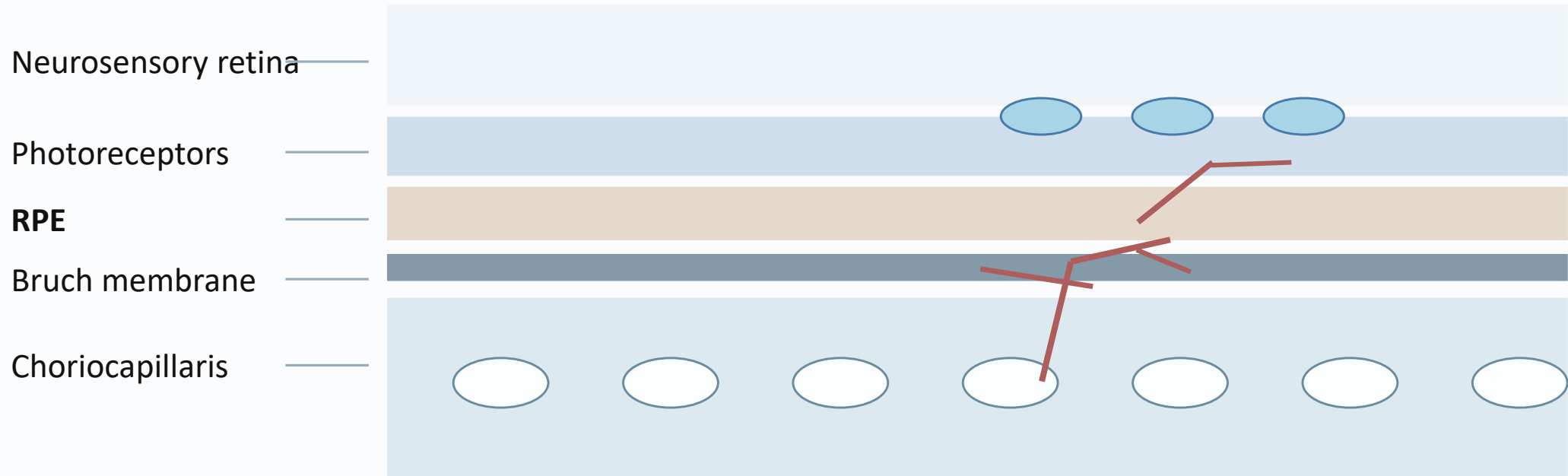
Neovascular membranes are leaky

- Neovessels may permit fluid to escape into adjacent retinal spaces.
- Fluid accumulation disturbs the architecture of the neurosensory retina.
- The corresponding clinical phenotype is termed exudative AMD.
- Leakage is a functional consequence of abnormal vascular growth.

Exudation

Wet AMD involves vascular permeability in addition to new-vessel formation.

Fluid from the neovascular lesion distorts the retina



Schematic — not a tissue section or OCT image

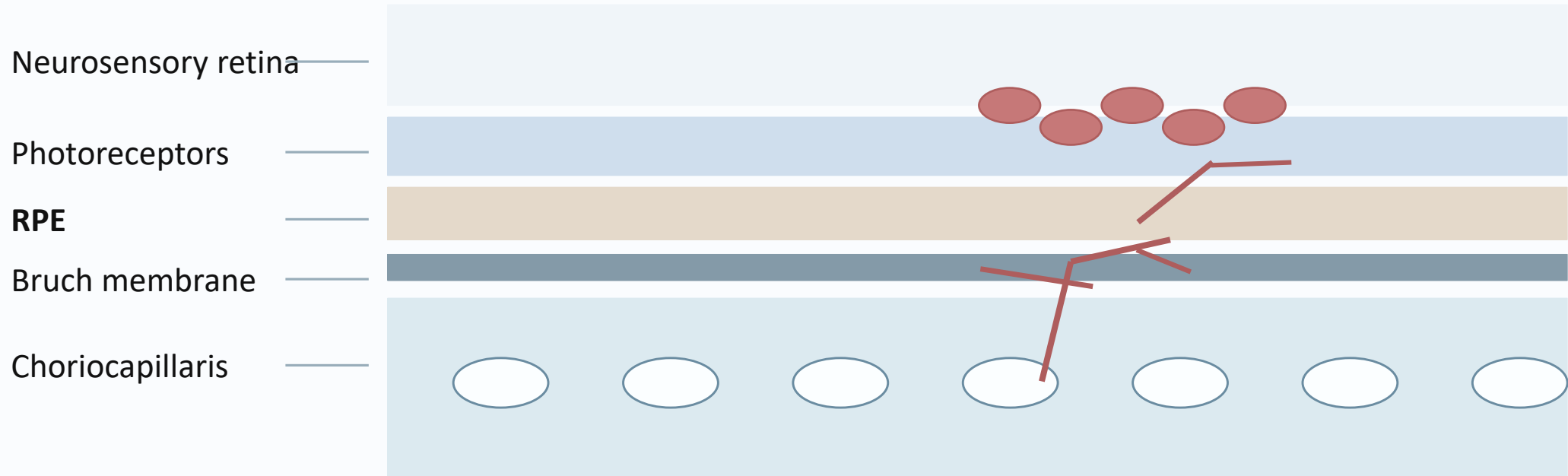
Hemorrhage complicates wet AMD

- Fragile neovascular vessels can hemorrhage.
- Exuded blood may accumulate around the macular neovascular membrane.
- Hemorrhage can abruptly degrade vision if critical macular regions are involved.
- The source describes both localized and unusually extensive bleeding.

Hemorrhage

Blood may be a major component of the neovascular lesion.

Subretinal blood: Pathologic location



Schematic — not a tissue section or OCT image

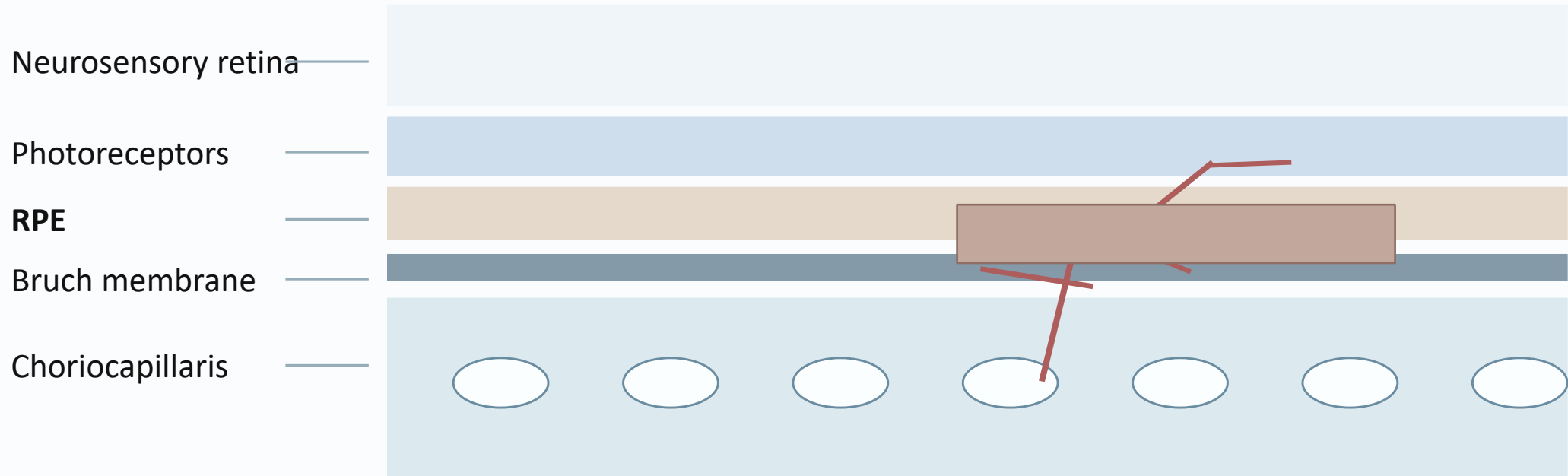
Organization of blood produces macular scarring

- The source describes exuded blood being organized by RPE cells.
- The outcome can be a macular scar.
- Scarring adds irreversible architectural distortion to vascular leakage.
- The lesion may remain functionally important after active fluid resolves.

Fibrous scar

Chronic organization converts an active exudative lesion into structural damage.

Scar tissue changes the outer retinal unit



Schematic — not a tissue section or OCT image

A large AMD hemorrhage can mimic a mass

- Some neovascular membranes produce a localized suffusion of blood.
- Marked hemorrhage may simulate an intraocular neoplasm clinically.
- The finding is a diagnostic pitfall, not evidence of an actual tumor.
- The underlying vascular lesion and full examination determine interpretation.

Diagnostic pitfall

Hemorrhagic appearance alone should not be called an intraocular tumor.

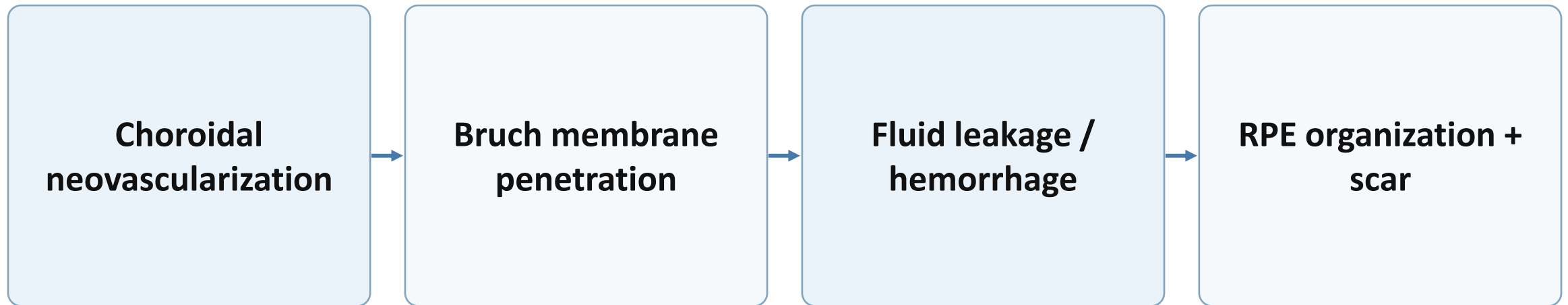
Extensive bleeding may reach the vitreous

- Diffuse vitreous hemorrhage as a possible complication.
- This is distinct from a small localized macular hemorrhage.
- Vitreous blood can obscure direct assessment of retinal lesions.
- The possibility follows from hemorrhage in the neovascular network.

Complication

Severe bleeding can obscure the retinal source.

Wet AMD: Injury sequence from neovascularization



Neovessels are the initiating morphologic distinction in this sequence.

Dry versus wet: Pathology-level comparison

Domain	Dry AMD	Wet AMD
Primary phenotype	Atrophic	Neovascular
Characteristic lesion	Drusen / geographic atrophy	Choroidal neovascularization
Blood leakage	Not defining	May be prominent
Tissue outcome	RPE + photoreceptor loss	Exudation, hemorrhage, scars
Specific therapy target	Complement in GA	VEGF-related angiogenesis

How either form reduces central vision

Dry AMD

Atrophy removes photoreceptors and outer-retinal support.

Wet AMD

Fluid, hemorrhage and scar disrupt the central retina.

Overlap

Coexisting lesions may contribute jointly to visual impairment.

AMD chiefly compromises central vision

- Visual symptoms reflect impairment of the macula.
- Patients may notice blurred or missing central detail.
- Activities requiring detailed straight-ahead vision become difficult.
- Peripheral vision can remain useful despite major central impairment.

Clinical pattern

Central visual dysfunction is the common clinical denominator.

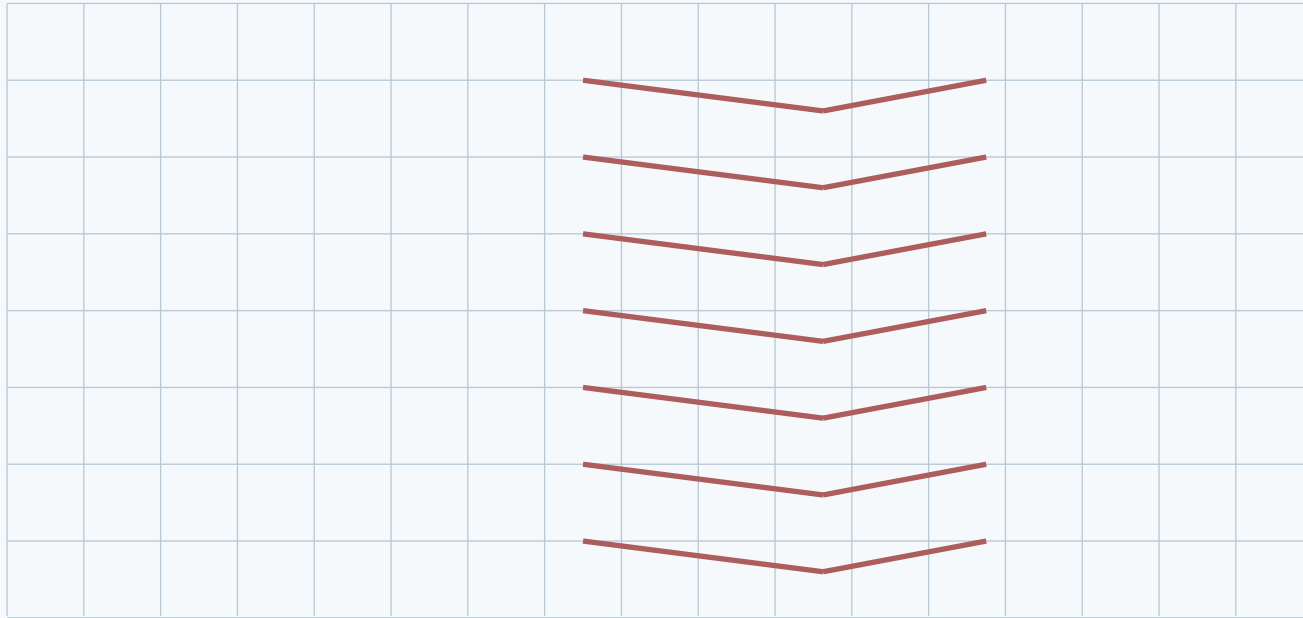
Early AMD can be asymptomatic

- Early structural changes may precede reported visual loss.
- Intermediate disease may produce mild central blurring.
- Difficulty seeing in dim light can occur.
- Symptom absence does not exclude macular disease.

Clinical limitation

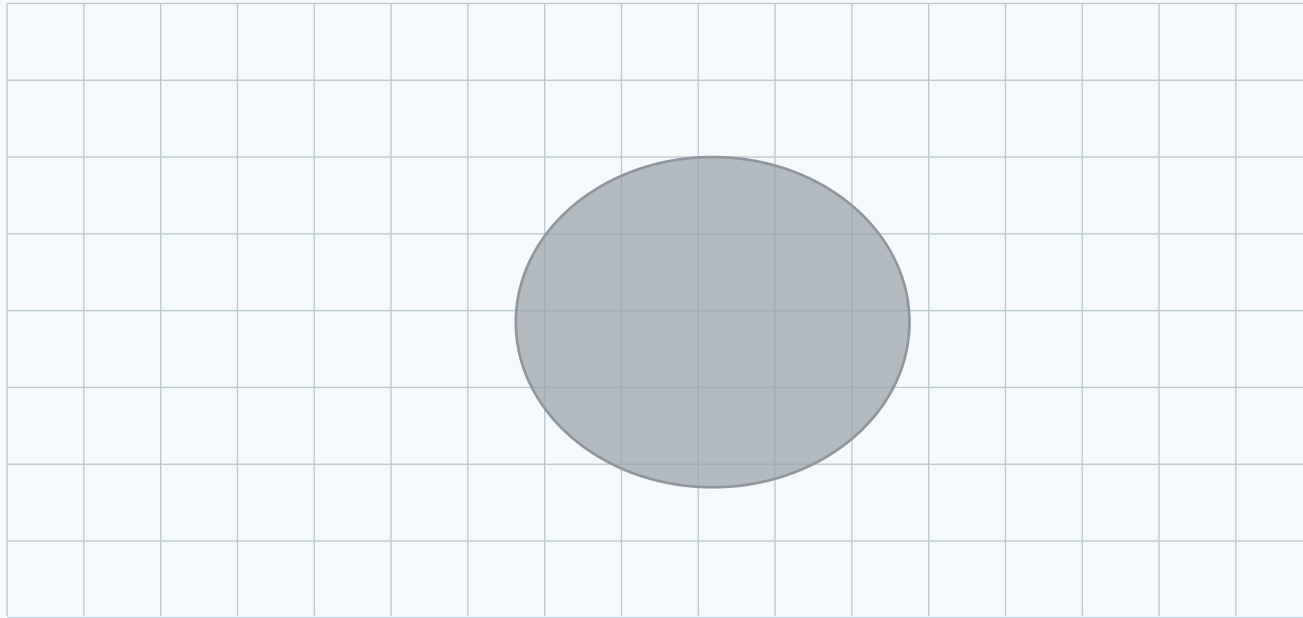
A macular examination can detect changes before the patient reports symptoms.

Metamorphopsia: Straight lines appear wavy



Schematic symptom representation

Central scotoma: Loss of the detailed field



Schematic symptom representation

Fundus examination connects symptoms with lesions

- Dilated fundus evaluation can identify macular pigmentary and atrophic changes.
- Drusen are a major finding in non-neovascular disease.
- Hemorrhage or exudation raises concern for neovascular activity.
- Findings should be correlated with the full clinical assessment.

Morphologic evidence

Examination locates the lesion rather than inferring it from symptoms alone.

OCT provides cross-sectional retinal information

- Optical coherence tomography (OCT) images retinal layers noninvasively.
- It can support evaluation of macular structural abnormalities.
- Fluid in or beneath the retina can suggest active exudation.
- An OCT image requires clinical interpretation; The diagram here is not an OCT scan.

Structural imaging

OCT adds depth information that fundus inspection alone cannot supply.

Conceptual OCT–histology correspondence

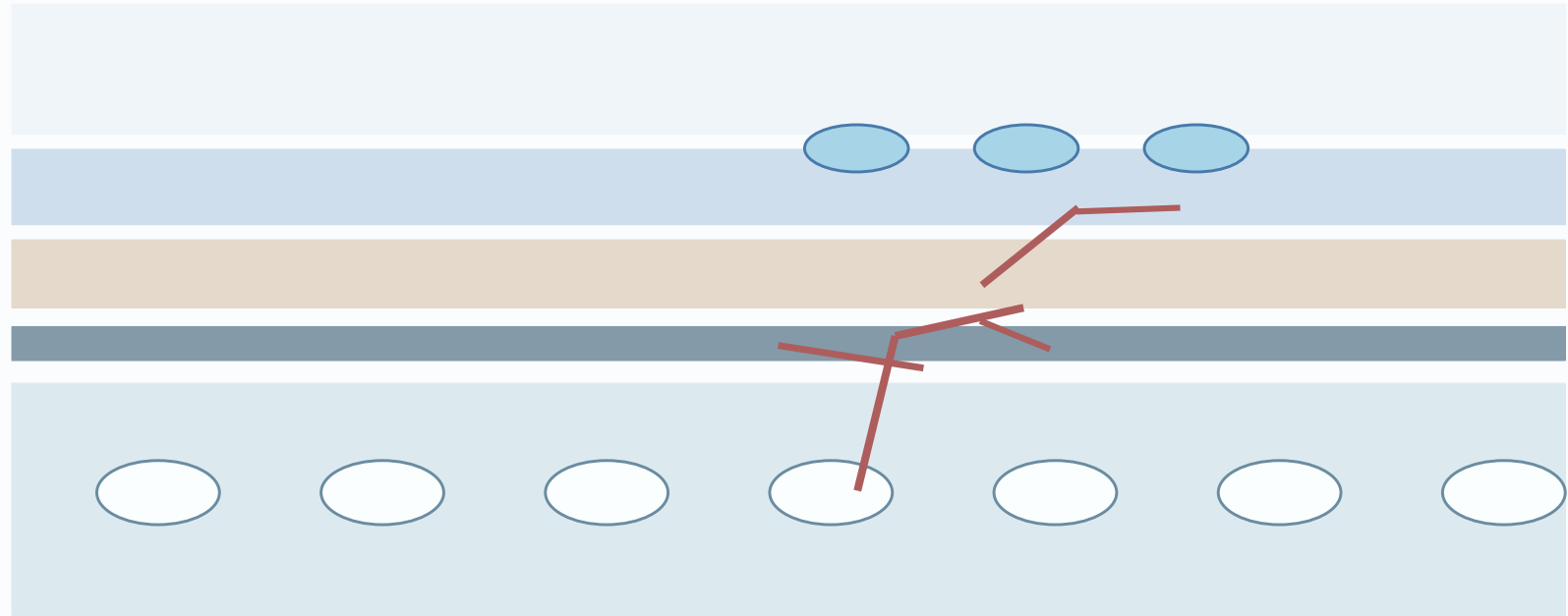
Neurosensory retina

Photoreceptors

RPE

Bruch membrane

Choriocapillaris



Schematic — not a tissue section or OCT image

Schematic only

A macular lesion should be classified by mechanism

Drusen + tissue loss

Favors a predominantly atrophic phenotype.

Abnormal vessels + fluid

Supports a neovascular mechanism.

Blood / scar

Consider the consequences of an active or healed neovascular lesion.

Anti-VEGF therapy addresses wet AMD biology

- Vascular endothelial growth factor (VEGF) promotes angiogenic signaling.
- Intravitreal VEGF antagonists as the mainstay of wet AMD treatment.
- Therapy targets pathologic neovascular activity and leakage.
- It does not directly replace atrophied photoreceptors.

Treatment mechanism

Suppressing vessel activity addresses wet AMD's defining lesion.

Why treatment is delivered intravitreally

Target tissue

The pathologic vessels are within the posterior ocular compartment.

Delivery route

Anti-VEGF agents are injected into the vitreous of the affected eye.

Goal

Control leakage and vision loss associated with neovascular activity.

Geographic atrophy: Complement inhibition

- Complement as a therapeutic target for geographic atrophy.
- NEI reports US approval of intravitreal C3 and C5 inhibitors in 2023.
- These drugs slow growth of atrophic lesions; They do not restore lost retinal tissue.
- Treatment selection requires considering potential benefits and adverse events.

Contemporary update

The therapeutic target follows from complement-associated injury.

Complement treatment has important tradeoffs

- Reducing atrophy expansion is different from reversing atrophy.
- NEI reports increased neovascular AMD risk with complement inhibitors.
- Additional serious inflammatory complications have been reported for some agents.
- Long-term benefit–risk and patient selection remain important.

Benefit ≠ cure

Rates of lesion growth and patient-centered visual outcomes are distinct.

RPE replacement is a regenerative research strategy

- Stem-cell-derived RPE replacement as a potential approach.
- The intended concept is restoration of an injured support-cell layer.
- Regeneration addresses a different goal than limiting complement activation.
- The source presents this as a future-oriented approach, not established routine therapy.

Research direction

Protecting remaining tissue and replacing lost tissue are different objectives.

Risk modification and early recognition

- Smoking is a modifiable AMD risk factor.
- A healthy lifestyle and regular eye assessment are part of NEI prevention messaging.
- New central distortion or blurred vision warrants prompt ophthalmic review.
- Macular disease can be present without symptoms in early stages.

Clinical prevention

Risk reduction and early examination complement mechanism-based treatment.

Case 1: Deposits and atrophy

An older adult has slowly progressive difficulty reading. The macula shows drusen and a well-demarcated area of outer-retinal atrophy.

Which AMD phenotype best explains the structural changes, and which tissue unit is affected?

Case 1: Morphologic reasoning

Classification

Dry / atrophic AMD

Evidence

Bruch membrane deposits
and geographic atrophy

Mechanism

Compromise of RPE,
photoreceptors and
choriocapillaris

Case 2: Exudation and hemorrhage

An older adult notices new distortion of straight lines. Macular examination suggests abnormal subretinal vessels with fluid and hemorrhage.

Which lesion defines the phenotype, and what mechanism should treatment target?

Case 2: Mechanism-based interpretation

Classification

Wet / neovascular AMD

Defining lesion

Choroidal neovascular
membrane penetrating
Bruch membrane

Therapeutic target

VEGF-mediated neovascular
activity

Pitfall: An obligatory dry-to-wet sequence

- It is incorrect to depict all wet AMD as end-stage dry AMD.
- Dry AMD is not always a precursor.
- Atrophy and neovascularization can also coexist.
- Identify the current lesion rather than applying a rigid timeline.

Correction

Parallel pathways and mixed morphologies explain the observed spectrum.

Integrated dry–wet review

Question	Dry AMD	Wet AMD
What accumulates or grows?	Drusen in Bruch membrane	New choroidal vessels
Where is the dominant injury?	RPE / photoreceptors / choriocapillaris	RPE–subretinal interface
Major end-stage lesion?	Geographic atrophy	Hemorrhage / macular scar
What is the target?	Complement-mediated progression in GA	VEGF-dependent neovascularization

Five pathology conclusions

- AMD is centered on the RPE–Bruch membrane–choriocapillaris unit.
- Dry AMD features drusen and geographic outer-retinal atrophy.
- Complement-associated susceptibility and inflammation are important but incompletely explained.
- Wet AMD is defined by choroidal neovascularization, leakage, bleeding and scar.
- Dry and wet lesions can coexist without a mandatory linear sequence.

Unifying principle

Anatomy explains both the phenotype and the principal therapeutic target.

Reference framework

Primary textbook

Robbins, Cotran & Kumar.
Pathologic Basis of Disease.
11th ed. 2026; Chapter 29,
pp. 1204–1206.

Clinical information

National Eye Institute: Age-
Related Macular
Degeneration (AMD);
diagnosis, symptoms and
care.

Treatment update

National Eye Institute: Story
of discovery—new dry AMD
drugs (December 12, 2023).